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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/051,034	03/31/98	MCKENZIE I	3164.98USWO

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EXAMINER	
BRUNOVSKIS,P	
ART UNIT	**PAPER NUMBER**
1632	12

DATE MAILED: 03/09/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/051,034	Applicant(s) McKenzie et al.
	Examiner Peter Brunovskis	Group Art Unit 1632

☒ Responsive to communication(s) filed on *Jan 24, 2000* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-25* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-25* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☒ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4, 5, 7, 8*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

Applicant's election with traverse of Group I, claims 1-25 in Paper No. 11 is acknowledged. The traversal is on the ground(s) that no previous unity of invention issues were raised in the PCT application, that the modified nucleic acids constitute a linking concept, and that no efficiency of searching is obtained by imposition of the restriction. This is not found persuasive for the following reasons:

First, the Office has complied with the PCT rules concerning unity of invention under 37 C.F.R. §1.475 and is not bound by the actions of the International Preliminary Examination Authority. Instant claims 1-25 recite modified nucleic acids, which, according to Applicants constitute a "linking concept which unifies all claims". However, 37 C.F.R. §1.475 (d) states that "[i]f multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application and the first recited invention of each of the other categories related thereto will be considered as the main invention in the claims, see PCT Article 17(3)(a) and 1.476(c)". In addition to the modified nucleic acids themselves, an individual pool of cells comprising the modified nucleic acids and transgenic *animals* comprising cells containing the modified nucleic acids constitute two additional, materially and patentably distinct inventions with different uses, e.g. in vivo/in situ/ex vivo gene therapy, organ transplantation, and/or animal model experimentation. The cells of the transgenic animals

comprising the modified nucleic acids have not been, nor can they be, claimed apart from its multicellular/multiorgan source. Furthermore, with respect to efficiency of searching, the Examiner has based the Restriction Requirement according to the PCT rules for U.S.C. 371 applications as set forth in 37 C.F.R. §1.475 and is not bound by the non-PCT guidelines of MPEP §803.

The requirement is still deemed proper and is therefore made FINAL.

Claim 22, as it is drawn to transgenic animals, organs, and cells therefrom, wherein every cell is modified by the nucleic acid of Group I, is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 11.

Specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: Claims 19 and 25 reciting "which cause it to be recognised as non-self by the recipient" and "wherein the carbohydrate is recognized as non-self by a species", respectively, both lack proper antecedent basis. The closest the specification comes to reciting this limitation is on p. 7, line 18-20: "Preferably said carbohydrate is capable of *stimulating* recognition of the cell as "non-self" by the immune system of an animal". The statements immediately following this

passage (e.g. p. 7, lines 20-23 and p. 8, lines 11-18) are much more conservative than the recitations of claims 19 and 25.

The disclosure is objected to because of the following informalities: "galactosylransferase" (p. 15, lines 24 and 27) and "fucosylransferase" (p. 15, line 25) are misspelled. Also, the specification recites "Example[s]" 2-5 without a heading for --Example 1--.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

In Figure 1, the diagrams for GT and ht-GT are identical even though they represent different constructions. Likewise, the diagrams for HT and gt-HT are identical even though they represent different constructions also.

Appropriate correction is required.

Claim Objections

Generally, the beginning of an independent claim should be preceded by --A-- (e.g. claim 1), and where appropriate, each dependent claim should be preceded by --The-- (see cl. 2-11, for example). An exception is where a dependent claim recites "a method...according to claim 1", for example, wherein claim 1 recites a product (e.g. cl. 17 should be --A method of producing *the*

nucleic acid--) or wherein a dependent claim is drawn to a product "produced by [the] method according to..." (see cl. 20 and 21, for example; thus, claim 21 should be changed to --An organ comprising *the* cell according to claim 20--).

In addition, where recited in the claims (and in the specification), the words "localisation" (e.g. claim 1, line), "localises" (e.g. claim 2, line 2), and "recognised" (e.g. claim 3, line 4) should conform to proper American English spelling and should be changed to "localization", "localizes", and "recognizes", respectively.

Claim 1 (and dependent claims) is objected to because of the following informalities: --wherein-- should be inserted between "cell" and "said" in line 5 and "when" (line 4) should be deleted. Also, "a" in line 7 should be changed to --the-- or --said-- (as in claim 17).

Claim 6 is objected to for using "or" instead of --and-- in line 4.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-14, 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 17-19 are rendered indefinite by their recitation of "a second glycosyltransferase" since it is unclear whether the "second glycosyltransferase" is obligated to encode a different enzyme, or whether it can embrace a different isoform relative to the "first" enzyme, or whether it can encompass the same enzyme from a different animal source, for example.

Claims 1, 18, and 19 are further rendered indefinite by their recitation "located in an area of the cell where it is able to compete for substrate" since the nature of the competition has not been defined (e.g. is it direct, indirect etc.), nor the location of the "second glycosyltransferase".

Claim 2 is rendered indefinite by its recitations of "to enable" and " to compete" since it is unclear *how* the localization signal "enable[s]" the catalytic domain "to compete" with the second glycosyltransferase for a substrate, and it is further unclear what the nature of the competition is and what the location of the second glycosyltransferase is (as pointed out for claim 1 above).

Claims 3, 5, 8, and 10 are rendered indefinite by their recitation of "derived from" since it is unclear how "derived from" is defined or what the structural relationship is between the initial product and the final product. For example, in claim 3 it is unclear whether the localization signal referred to is obligated to "derive from" any particular species-specific glycosyltransferase. It is further noted that the definition of "derived from", as recited on p. 5, line 25 and as applied to catalytic domains, does not apply to the localization signals of instant claims 3, 5, 8, and 10.

Claim 6 is rendered indefinite by its recitation of "galactosyl sulphating enzyme" and "phosphorylating enzyme" since there is no evidence on record suggesting these enzymes are

glycosyltransferases, nor are there any specific examples of such enzymes given that would qualify as glycosyltransferases.

Claim 7 is rendered indefinite by its recitation of "originates from" since it is unclear how "originates from" is defined or what the structural relationship is between the mammal and the recited domains.

Claim 8 recites the limitation "is intended to transform" in lines 3 and 4. There is insufficient antecedent basis for this limitation in the claim. Claim 8 is also rendered indefinite by its recitation of "species" since it is unclear whether "species" refers to the nucleic acid or the cell.

Claims 9 and 16 are rendered indefinite by their recitation of "Gal transferase" and "gal-transferase", respectively, since it is not clear whether the recitation of "Gal transferase" or "gal-transferase" is limited to the α (1,3)-galactosyltransferase described in the specification (p. 2, line 23) or whether it can encompass other galactosyltransferases, since the term "Gal-transferase" has been used in the art in a general way to refer to other *species* of "Gal-tranferase", such as β (1,4)-galactosyltransferase, for example.

Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language. This claim is an omnibus type claim.

Claims 18 and 19 are rendered indefinite by the recitation "capable of producing said carbohydrate" since glycosyltransferases are not capable of *producing* carbohydrates, only *transferring* them (see p. 5, lines 23 and 24).

Claim 23 (and dependent claims) recites the limitation "in a cell" in line 2. There is insufficient antecedent basis for this limitation in the claim. Furthermore the claim is incomplete since the method steps don't clearly relate back to the preamble. Claim 24 lists examples of "expression unit" that include both DNAs and cells. However, claim 23 recites "[A]n expression unit which expresses a nucleic acid according to claim 1, resulting in a cell". Neither DNAs nor cells are capable of "resulting in a cell which is...".

Claim 25 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language. This claim is an omnibus type claim. Additionally, the claim is rendered indefinite by its recitation "under conditions such that the chimeric enzyme is produced" since the "conditions" that would meet the limitations of this claim have not been defined in the disclosure.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 11 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The application discloses a nucleic acid encoding gtHT that is encompassed by the definitions for **biological material** set forth in 37 C.F.R. § 1.801. Because it is apparent that this biological material is essential for practicing the claimed invention, it must be obtainable by a reproducible method set forth in the specification or otherwise be known and readily available to the public as detailed in 37 C.F.R. §§ 1.801 through 1.809.

It is unclear whether this biological material is known and readily available to the public or that the written instructions are sufficient to reproducibly construct this biological material from starting materials known and readily available to the public. Accordingly, availability of such biological material is deemed necessary to satisfy the enablement provisions of 35 U.S.C. § 112. If this biological material is not obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the biological material. In order for a deposit to meet all criteria set forth in 37 C.F.R. §§ 1.801-1.809, applicants or assignee must provide assurance of compliance with provisions of 37 C.F.R. §§ 1.801-1.809, in the form of a declaration or applicant's representative must provide a statement. The content of such a declaration or statement is suggested by the enclosed attachment. Because such deposit will not have been made prior to the effective filing date of the instant application, applicant is required to submit a verified statement from a person in a position to corroborate the fact, which states that the biological material which has been deposited is the biological material specifically identified in the application as filed (37 C.F.R. § 1.804). Such a statement need not be verified if the person is an agent or attorney registered to practice before the Office. Applicant is also reminded that the specification must

contain reference to the deposit, including deposit (accession) number, date of deposit, name and address of the depository, and the complete taxonomic description.

Claims 1-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being in principle enabling for *specific* chimeric glycosyltransferases, such as gtHT and pgtHT, it does not reasonably provide enablement for the broad scope of chimeric glycosyltransferases exemplified in claims 1, 6, 7, 8, and 17-19. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining enablement are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation....Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (Wands, 8 USPQ2d 1404). Factors that can be used in evaluating undue experimentation include: the quantity of experimentation necessary, the amount or direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

Nature of the invention and state of the prior art. The claimed invention describes functionally active chimeric enzymes comprising the amino terminal "tail" of porcine α-1,3-galactosyltransferase (GT) fused to catalytic domains of either human α-1,2-fucosyltransferase (HT; resulting in gtHT) or pig α-1,2-fucosyltransferase (resulting in pgtHT; Example 4, p. 21) or the amino terminal "tail" of HT fused to the catalytic domain of GT (resulting in htGT). The broad claims cover virtually any nucleic acid encoding a chimeric enzyme comprising a glycosyltransferase localization signal fused to a glycosyltransferase catalytic domain. The fact that the chimeric enzyme carries a localization signal from a second glycosyltransferase provides sufficient grounds for the enzyme "to compete for substrate" with a second glycosyltransferase since the chimeric enzyme is expected to be colocalized with the glycosyltransferase from which the localization signal was derived (and other "second" chimeric enzymes of the same type as well). However, claim 1 does not require that the localization signal to be functional in all cells; the resulting chimeric enzyme can at least compete for substrate with members of its own kind sharing a common localization, whatever it may be.

Localization signals for Golgi retention in glycosyltransferases do not follow uniform rules. Different glycosyltransferases exhibit different requirements regarding the composition of amino-terminal sequences (e.g. cytoplasmic tail, transmembrane domain, stem, and/or post-translational modifications) for Golgi retention, localization, and subcompartmentalization (see Colley, Glycobiology, 7:1-13, 1997; Fig. 1, p. 3 and Machamer, Curr. Opin. Cell Biol., 5:606-612, 1993; Table 1, p. 608). For example, whereas the transmembrane domain of β-1, 4-

galactosyltransferase (β-1, 4-GalT) and N-acetylglucosaminyltransferase I (GlcNAcTI) have been shown to be responsible for their differential localizations in the TGN/tran-Golgi and medial-Golgi cisternae, respectively, the structural requirements for α2,6 sialyltransferase localization in the TGN is more uncertain (Gleeson et al., Glyconconj. J., 11:381-394, 1994; p. 384, left column, 1st full paragraph). Subtle, poorly defined cell type specific differences in cisternal environments associated with Golgi subcompartmentalization (e.g. medial-Golgi, trans-Golgi, and trans-Golgi network; TGN) have also been observed for certain glycosyltransferases (Colley, p. 5, left column, first full paragraph). For example, GlcNAcTI has been localized within the medial or medial and trans Golgi cisternae of different cell types (Colley, p. 5, right column, 1st sentence). Such findings underscore the importance in understanding how differences in cisternal environments in different cell types relates to the different types of Golgi localization domains above (Colley, p. 5, left column, last sentence of first full paragraph). As stated in Gleeson et al.: "it is apparent that the localization of glycosyltransferases does not involve a discrete retention signal but may be dependent on many interactions spanning the length of the molecule" (p. 392, last paragraph). The specification does not teach one of ordinary skill in the art how to identify localization signals for use in the claimed invention, nor does it fully teach how to use the chimeric enzyme constructions unable to *appropriately* colocalize the enzyme in *all* candidate organs for xenotransplantation. Further complicating Golgi localization of glycosyltransferases is based on the oligomerization/kin recognition model, wherein localization is highly sensitive to concentration of enzyme (see Colley, pp. 9-10). Presently, it remains to be seen whether the

chimeric enzymes containing hybrid catalytic domains would be capable of forming oligomers coincident with retention according to the oligomerization/kin recognition model wherein the localization signal is able to meet the limitations of qualifying as a localization signal as taught in the specification (i.e. "responsible for anchoring it in location within the cell", p. 5, line 33).

Guidance and working examples. In the instant application, the only embodiment described with any functionally demonstrable utility is that corresponding to the catalytic domain of α-1,2-fucosyltransferase fused to the amino tail of α-1,3-galactosyltransferase (gtHT; pp. 15-20 and p. 24, Table 1). In monkey kidney cell (COS) transfectants, altered patterns of glycosylation were observed between gtHT and its opposite counterpart, ht-GT (Table 1, p. 24). The specification does not teach one of ordinary skill in the art how to make and use any other chimeric enzyme in the practice of the claimed invention. In addition, the specification does not teach how to identify appropriate localization signals and/or catalytic domains for a given glycosyltransferase, nor does it teach how to identify or obtain such signals/domains from the broad range of embodiments comprising glycosyltransferases from "a mammal selected from the group consisting of human, primates, ungulates, dogs, mice, rats and rabbits" (cl. 7). Furthermore, apart from α-1,3-galactosyltransferase, the specification does not describe any other glycosyltransferase for use in the claimed invention that "produces glycosylation patterns which are recognized as foreign by a transplant recipient" (cl. 3). Moreover, the specification does not teach how to make and use the claimed invention wherein the "the first glycosyltransferase is

selected from the group consisting of...secretor sialyltransferase, a galactosyl sulphating enzyme or a phosphorylating enzyme (cl. 6).

Apart from the non-elected subject matter drawn to transgenic animals and organs therefrom, there is little or no guidance teaching one of ordinary skill in the art how to use the cells or "expression units" (and methods for their production) covered by claims 19-25 for ex vivo gene therapy. It is further noted that successful use of gene therapy was not routinely obtainable by those skilled in the art at the time the instant application was filed. W. French Anderson, one skilled in the art, recently concluded: "[e]xcept for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human diseases [Nature, vol. 392:(Supp.), 1998, p. 25, first paragraph]...[s]everal major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered.

Predictability of the art. The physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Based on the lack of uniformity and knowledge concerning Golgi localization signals as described above, it is difficult to identify appropriate localization signals and/or catalytic domains for a given glycosyltransferase. Consequently, it appears unreasonable to suggest that one of ordinary skill in the art could construct the nucleic acids encompassing the broad range of embodiments in the claimed invention or use them for ex vivo gene therapy without undue experimentation.

Amount of experimentation necessary. Given the unpredictable and undeveloped state of the art as described above, it would likely require considerable experimentation to develop the claimed products and methods for the purposes of the claimed invention.

For the reasons discussed above, it would require undue experimentation for one skilled in the art to make and use the claimed invention. This is particularly true given the state of the art, the nature of the invention, the scarcity of guidance and working examples in the specification, the unpredictability of the art, and the amount of experimentation necessary.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 8, 12-15, 17-20, and 23 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Schwientek et al (J. Biol. Chem., 271(7):3398-3405, 1996).

Schwientek et al. disclose a gene fusion comprising a localization signal from the membrane anchor region of a yeast glycosyltransferase, Mnt1p, fused to the soluble form of human β-1,4-galactosyltransferase (see sentence abridging pp. 339803399), further comprising a catalytic domain from the latter. One of the stated goals of the disclosure was to enable construction of yeast strains for that secrete desired glycoforms of applied proteins with limited production of mannose residues which are known targets for mannose-binding proteins and specific antibodies (p. 3399, left column, lines 10-13).

Claims 15 and 16 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Sandrin et al (Xenotransplantation, 1:81-88, 1994).

Sandrin et al. disclose a cDNA clone for α-1,3-galactosyltransferase, pPGT-2, wherein the amino terminus comprises a localization signal (p. 82, last sentence abridging left and right columns and Fig. 1, p. 83).

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX number is (703) 308-4242 or 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO

DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter Brunovskis whose telephone number is (703) 305-2471. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached at (703) 308-2035.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Peter Brunovskis, Ph.D.
Patent Examiner
Art Unit 1632
March 6, 2000

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER

SUGGESTION FOR DEPOSIT OF BIOLOGICAL MATERIAL ATTACHMENT

A declaration by applicant or assignee, or a statement by applicant's agent identifying a deposit of biological material and averring the following may be sufficient to overcome an objection or rejection based on a lack of availability of biological material. Such a declaration:

1. Identifies declarant.

2. States that a deposit of the material has been made in a depository affording permanence of the deposit and ready accessibility thereto by the public if a patent is granted. The depository is to be identified by name and address. (See 37 C.F.R. § 1.803).

3. States that the deposited material has been accorded a specific (recited) accession number.

4. States that all restrictions on the availability to the public of the material so deposited will be irrevocably removed upon the granting of the patent. (See 37 C.F.R. § 1.808(a)(2)).

5. States that the material has been deposited under conditions that assure that access to the material will be available during the pendency of the patent application to one determined by the Commissioner to be entitled thereto under 37 C.F.R. § 1.14 and 35 U.S.C. § 122. (See 37 C.F.R. § 1.808(a)(1)).

6. States that the deposited material will be maintained with all the care necessary to keep it viable and uncontaminated for a period of at least five years after the most recent request for the furnishing of a sample of the deposited microorganism, and in any case, for a period of at least thirty (30) years after the date of deposit or for the enforceable life of the patent, whichever period is longer. See 37 C.F.R. § 1.806).

7. That he/she declares further that all statements made therein of his/her own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon.

Alternatively, it may be averred that deposited material has been accepted for deposit under the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure (e.g., see 961 OG 21, 1977) and that all restrictions on the availability to the public of the material so deposited will be irrevocably removed upon the granting of a patent.

Additionally, the deposit must be referred to in the body of the specification and be identified by deposit (accession) number, date of deposit, name and address of the depository, and the complete taxonomic description.

Application No.: 09/051,034

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [ ] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- [ ] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [ ] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [X] 7. Other: "Sequence Listing" is incomplete, see page 13, lines 19, 20, 24, 29, and 33; page 20, lines 5 and 35; page 21, lines 30 and 33; Figure 6, Figure 7

Applicant Must Provide:

- [X] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- [X] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- [X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
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